REMARKS

In view of the following remarks, the Office is requested to allow Claims 1-11, 17-20, and 39-46, the only claims pending and under examination in this application.

Claim Rejections - 35 U.S.C. § 103

Claims 1, 4, 7, 9, 10, 17, 18, 20, 39-42, 45 and 46 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rezai (US Publication No. 2005/0065574) in view of Ideker et al. (5,552,854).

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. See, e.g., KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1740 (2007); Pharmastem Therapeutics v. Viacell et al., 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1). In addition to demonstrating that all elements were known in the prior art, the Office must also articulate a reason for combining the elements. See, e.g., KSR at 1741; Omegaflex, Inc. v. Parker-Hannifin Corp., 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) citing KSR. Further, the Supreme Court in KSR also stated that that "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." KSR at 1740; emphasis added. As such, in addition to showing that all elements of a claim were known in the prior art and that one of skill had a reason to combine them, the Office must also provide evidence that the combination would be a predicted success.

The rejected claims are directed to a method of treating a female subject known to suffer from a fertility condition. The method includes modulating at least a portion of the autonomic nervous system of the female subject to increase the sympathetic activity/parasympathetic activity ratio so as to treat a female subject for a fertility condition. The method further includes determining the ratio of

sympathetic activity to parasympathetic activity prior to the modulation and performing the modulation of a portion of the autonomic nervous system based on the determined ratio of sympathetic activity to parasympathetic activity.

In maintaining the rejection, the Office alleges that Rezai's invention is capable of increasing the sympathetic/parasympathetic activity ratio of the subject. For evidence that hypothalamus stimulation will result in increasing the ratio, the Office again cites Maillard (U.S. Patent 4,339,384). The Office further alleges that although Rezai does not disclose determining a ratio of sympathetic activity to parasympathetic activity, Ideker, et al. allegedly teach sensing a ratio of sympathetic and parasympathetic nervous system conduction (Office Action, p. 3-4).

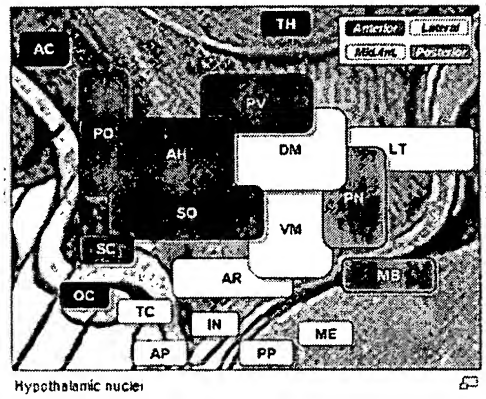
The Applicants respectfully disagree with this assertion. The Applicants maintain that neither Rezai nor Ideker contains the element of *increasing the sympathetic activity/parasympathetic activity ratio in a manner effective to treat a female subject for a fertility condition.* The disclosure in Rezai merely teaches stimulation of the hypothalamus for treatment of a wide variety of conditions. There is no disclosure in Rezai of determining or increasing a ympathetic/parasympathetic ratio in a manner effective to treat a subject. The Office alleges that "Rezai does increase the sympathetic activity/parasympathetic activity ratio, regardless of whether this effect was realized at the time, as evidenced by Maillard (col. 8, lines 33-36)" (Final Office Action, p. 7). However, the Applicants contend that the cited portion of Maillard merely states that "electric stimulation of the posterior hypothalamus induces an intense activation of the sympathetic system and of the dysrhythmias". Rezai, on the other hand, discloses on p. 1, col. 2, paragraph [0005]:

> Specifically, the present invention relates to implanting a stimulator, which can be either an electrode or catheter, into a target site of a hypothalamic-associated circuitry, a hypothalamus, a division of a hypothalamus, or a nucleus of a hypothalamus to electrically and/or chemically stimulate the target site to modulate the target site to affect the hypothalamic-related condition.

In other words, the stimulation in Rezai can be any part of the hypothalamus, not just the posterior hypothalamus. Maillard merely mentions stimulation of the posterior hypothalamus, which includes the medial and lateral nuclei. Maillard does not disclose stimulation of the anterior region of the hypothalamus, which includes both medial and lateral areas, or the tuberal region of the hypothalamus, which includes the medial and lateral areas, as shown in the chart below:

The hypothalamic nuclei include the following:[3][4][5]

Region	Area	Nucleus	Function[6]
Anterior	Medial	Medial preoptic nucleus	• urinary bladder contraction • Decreased heart rate • Decreased blood pressure
		Supraoptic nucleus (SO)	• oxytocin release • vasopressin release
		Paraventricular nucleus (PV)	• oxytocin release • vasopressin release[7]
		Anterior hypothalamic nucleus (AH)	• thermoregulation • panting • sweating • thyrotropin inhibition
		Suprachiasmatic nucleus (SC)	• vasopressin release • Circadian rhythms
	Lateral	Lateral preoptic nucleus	
		Lateral nucleus (LT)	• thirst and hunger
		Part of supraoptic nucleus (SO)	• vasopressin release



Hypothalamic nuclei

Tuberal	Medial	Dorsomedial hypothalamic nucleus (DM)	• GI stimulation
		Ventromedial nucleus (VM)	• satiety • neurendocrine control
		Arcuate nucleus (AR)	• Lutenizing Hormone R.H. release • Follicle Stimulating Hormone Releasing Factor • feeding
	Lateral	Lateral nucleus (LT)	• thirst and hunger
		Lateral tuberal nuclei	
Posterior	Medial	Mammillary nuclei (part of mammillary bodies) (MB)	• memory
		Posterior nucleus (PN)	• Increase blood pressure • pupillary dilation • shivering
	Lateral	Lateral nucleus (LT)	

(Wikipedia; accessed 3/23/2009)

Therefore, even if, as the Office alleges, "Rezai does increase the sympathetic activity/parasympathetic activity ratio, regardless of whether this effect was realized at the time", the Office has supplied evidence only to the extent that this applies to stimulation of the posterior hypothalamus. The Office has not provided sufficient evidence that the methods in Rezai would *necessarily* result in an increase in the sympathetic activity/parasympathetic activity ratio, because the methods in Rezai are not limited to stimulation of the posterior hypothalamus, and because Rezai also does not specifically disclose stimulation of the sympathetic nervous system. There is therefore no disclosure in Rezai of determining or increasing a sympathetic/parasympathetic ratio in a manner effective to treat a subject.

The Office therefore relies on Ideker for this element. However, Ideker is directed to a method for preventing arrhythmia by afferent nerve stimulation. To the extent that Ideker discloses determining the ratio of sympathetic nerve activity to parasympathetic nerve activity, it is for the purpose of detecting a high risk of arrhythmia (col. 1, lines 53 to 56). Further, in determining the ratio of sympathetic

to parasympathetic nerve activity, Ideker discloses that it is a subject's heart rate variability that is measured (col. 3, lines 49 to 52). Additionally, to the extent that Ideker discloses stimulating a nerve it is an afferent nerve to the heart or central nervous system (col. 2, lines 60 to 62). Hence, there is no suggestion in Ideker of *increasing the sympathetic activity/parasympathetic activity ratio in a manner effective to treat a subject,* and no disclosure of treating fertility. Therefore, the Applicants maintain that as neither Rezai nor Ideker teach the element of increasing the sympathetic activity/parasympathetic activity ratio of a subject in a manner effective to treat a female subject for a fertility condition, the combination of the references fails to anticipate all the elements of the current claims.

Furthermore, the Office has not articulated a sufficient reason why one of skill in the art would use the method in Rezai with the ratio of Ideker, because Rezai discloses using only a simple measurement of neuronal activity, and not a ratio. The Office alleges that using Ideker's variable (sympathetic/parasympathetic ratio) in place of the "rate and pattern of neuronal activity" disclosed in Rezai is a "simple substitution" (Office Action, p. 8). However, the Applicants again contend that the "sensor signal" for the closed-loop feedback mechanism disclosed in Rezai is a simple measurement, such as synaptic potential (paragraphs [0047] and [0048]). Rezai in fact discloses a long list of potential "sensor signals", as follows:

> "Such physiological activity to be detected is a physiological characteristic or function of the body, and includes, for example, body temperature regulation, blood pressure, metabolic activity, cerebral blood flow, pH levels, vital signs, galvanic skin responses, electrocardiogram, electroencephalogram, action potential conduction, and hormone, electrolyte, glucose or other chemical production." (see paragraph [0047], lines 14-21)

The list of "sensor signals" in Rezai are simple measurements, e.g., blood pressure, or electrocardiogram. There is no disclosure in Rezai of determining a ratio of neuronal activity, which would require a measure of sympathetic activity, a measure of parasympathetic activity, and then comparing the two measures to determine a ratio. In fact, Rezai even discloses that "if the hypothalamic-related

condition is arrhythmias, bradycardia, or angina, then sensors may be placed on the skin to measure electrocardiograms" (paragraph [0051], lines 17-19) In other words, even if the condition is an arrhythmia, as in Ideker, the suggested "feedback" in Rezai is a skin sensor to measure an electrocardiogram, i.e., a simple measurement of neuronal activity. There is simply no suggestion in Rezai of using a ratio of any kind.

In response to this argument, the Office has alleged that "the examiner is not relying in any way on Rezai's arrhythmia embodiment. Although combining various embodiments of Rezai with various embodiments of Ideker may or may not result in the claimed subject matter, the examiner is relying on Rezai's fertility-treating embodiment using closed-loop feedback of neuronal activity patterns" (Final Office Action, p. 8)

However, the Applicants contend that "[t]he Examiner has the initial burden of establishing a prima facie case of obviousness. See *In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984); *In re Rinehart*, 531 F.2d 1048, 1051 (CCPA 1976). The reasoning relied upon by the Examiner must not come solely from the description of the Appellants' invention in their Specification. If it does, the Examiner used impermissible hindsight when rejecting the claims. See W.L. Gore & Associates v. Garlock, Inc., 721 F.2d 1540, 1553 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984); *In re Rothermel*, 276 F.2d 393, 396 (CCPA 1960)." (See BPAI decision of 1/15/2009 *Ex parte* Vogel, Ognibene, Bench, and Peaslee; Appeal 2008-5921)

The Applicants maintain that the Office has not shown sufficient reason why one of ordinary skill in the art would have been led by the disclosure in Rezai's fertility-treating embodiment (using a feedback of a simple measurement of neuronal activity) with a ratio as disclosed in Ideker, which is furthermore a ratio for the purpose of detecting a high risk of arrhythmia. Additionally, even if the Office is solely relying on "Rezai's fertility-treating embodiment using closed-loop feedback

of neuronal activity patterns", it is unclear to the Applicants why one of ordinary skill in the art would combine the "fertility-treating embodiment" of Rezai with the ratio in Ideker, rather than the "arrthythmia-treating embodiment" actually disclosed in Rezai, in which the suggested feedback is a skin sensor to measure an electrocardiogram, i.e., a simple measurement of neuronal activity, as discussed above.

It appears to the Applicants that the Office does not have support in Rezai's disclosure for the combination with Ideker. In fact, the reasoning relied upon by the Office for combining the two references appears to derive solely from the description of the Applicant's invention in their specification. The Office appears to be proposing a modification of the "fertility-treating embodiment" of Rezai's method by using the sympathetic activity/parasympathetic activity ratio for detecting a high risk of arrhythmia disclosed in Ideker, despite the fact that 1) Rezai does not disclose using a ratio; and 2) even in the case of an arrthymia, Rezai teaches using a skin sensor electrocardiogram, not a ratio, for the feedback loop. The Examiner's rationale for modifying Rezai's method with the ratio of Ideker therefore appears to be based upon impermissible hindsight.

Additionally, with respect to Claims 45 and 46, the Office states that neither Rezai nor Ideker disclose treatment for a period of days or weeks, however that it is well known to treat disorders of the human estrus cycle for a period of days to weeks (Final Office Action, p. 8). The Applicants maintain, however, that the disclosure in Rezai merely teaches that stimulation of the hypothalamus for a wide variety of conditions may be continuous or intermittent (paragraphs 0041 and 0042). There is no disclosure in Rezai of modulation for a period of days or weeks. The addition of Ideker does not remedy this deficiency, because Ideker also only discloses that stimulation may be performed continuously or intermittently to prevent the reoccurrence of an arrhythmia after delivery of the electric pulse (col. 3, lines 17-20). The Office has additionally cited Bothe Loncar, paragraph [0264] as one of the many teachings of modulating fertility function over a period of days or

weeks. However, Bothe Loncar discloses that "[f]our different specific discrete skin areas are to be stimulated throughout the menstrual cycle...during the proper days throughout the cycle". However, it is not clear that that this represents either a period of days, or a period of weeks. As none of the references discloses the element of modulation for a period of days or weeks, the combination of Rezai and Ideker fail to render Claims 45 and 46 obvious.

Therefore, as discussed above, the Applicants maintain that neither Rezai nor Ideker teach the element of *increasing the sympathetic activity/parasympathetic activity ratio in a manner effective to treat a female subject for a fertility condition.* Rezai does not disclose the element of a sympathetic activity/parasympathetic activity ratio, and Ideker mentions a ratio only to detect a risk for arrhythmia, not to treat fertility. The combination therefore does not contain all the elements of the claimed invention, and does not render the claimed invention obvious. In addition, the Office has not articulated a sufficient reason why one skilled in the art would have modified the method in Rezai with the ratio in Ideker. At most, if one of skill in the art were motivated to modify Rezai in view of Ideker, it would be for the purpose of treating arrhythmia and not a female fertility condition.

In view of the above, the Applicants contend that a *prima facie* case of obviousness has not been established, and consequently, the Applicants respectfully request that the Office reconsider and withdraw the 35 U.S.C. § 103(a) rejection of Claims 1, 4, 7, 9, 10, 17, 18, 20, 39-42, 45 and 46

Claims 2 and 3 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Rezai in view of Ideker, as applied to Claim 1 above, or, in the alternative, over Rezai and Ideker and further in view of Bothe Loncar et al. (US Publication No. 2002/0188336).

As set forth above, elements of the rejected claims are directed to a method of treating a female subject known to suffer from a fertility condition. The method includes determining a sympathetic activity/parasympathetic activity ratio and modulating at least a portion of the autonomic nervous system based on the determined sympathetic activity/parasympathetic activity ratio so as to treat the female subject for the fertility condition.

As discussed above, Rezai does not disclose determining a ratio of sympathetic activity to parasympathetic activity. Furthermore, the Office has not articulated a sufficient reason to combine Rezai with Ideker in the manner suggested. At most, if one of skill in the art were motivated to modify Rezai in view of Ideker it would be for the purpose of treating arrhythmia and not a female fertility condition. Therefore, the combination of Rezai and Ideker does not teach or suggest all the claim limitations. As Bothe Loncar is cited solely for its alleged disclosure of modulating the autonomic nervous system during the luteal phase of the menstrual cycle, it fails to remedy this deficiency.

Therefore, a *prima facie* case of obviousness has not been established because the combination of Rezai in view of Ideker and further in view of Bothe Loncar fails to teach or suggest all the claimed limitations, namely, increasing the sympathetic activity/parasympathetic activity ratio in a manner effective to treat a female subject for a fertility condition, wherein the modulation is based on the determined sympathetic activity/parasympathetic activity ratio. The Applicants' therefore respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 2 and 3 be withdrawn.

Claims 5, 6, 11, 43 and 44 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rezai in view of Ideker, as applied to Claim 1 above, or, in the alternative, over Rezai and Ideker and further in view of Whitehurst et al. (USPN 6,832,114).

Claims 5, 6, 11, 43 and 44 depend from Claim 1. As set forth above, Claim 1 is directed to a method of modulating at least a portion of the autonomic nervous system of a female subject to increase the sympathetic activity/parasympathetic activity ratio so as to treat the female subject for a fertility condition.

As described above, Rezai discloses affecting a "hypothalamic-related condition" by electrically or chemically stimulating the hypothalamus (see Abstract), and discloses a list of over 55 conditions allegedly related to the hypothalamus (page 9, Table II). However, Rezai does not disclose determining the sympathetic activity/parasympathetic activity ratio of a subject and modulating the ANS of the subject based on the determined sympathetic activity/parasympathetic activity ratio. Furthermore, the Office has not articulated a sufficient reason to combine Rezai with Ideker in the manner suggested. At most, if one of skill in the art were motivated to modify Rezai in view of Ideker it would be for the purpose of treating arrhythmia and not a female fertility condition.

The addition of Whitehurst et al. does not cure the deficiency of Rezai. Whitehurst et al. disclose modulating a patient's pancreatic endocrine secretion by electrical stimulation to treat diabetes. However, Whitehurst et al. do not disclose determining the sympathetic activity/parasympathetic activity ratio of a subject and modulating at least a portion of the autonomic nervous system of the subject to increase the sympathetic activity/parasympathetic activity ratio of the subject.

Additionally, nowhere in Whitehurst is there the element of wherein the electrical inhibition comprises ablation, as in Claim 44. Since the combination of Rezai, Ideker, or Whitehurst et al. does not disclose this claim element, the references, either alone or combined, do not teach or suggest all the claim limitations of Claim 44.

In view of the above, the Applicants contend that a *prima facie* case of obviousness has not been established because the combination of Rezai in view of Ideker and further in view of Whitehurst fails to teach or suggest all the claimed limitations, namely modulating at least a portion of the autonomic nervous system of a female subject to increase the sympathetic activity/parasympathetic activity ratio in manner effective to treat a female subject for a fertility condition, wherein the modulation is based on the determined sympathetic activity/parasympathetic activity ratio. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 5, 6, 11, 43 and 44 be withdrawn.

Claim 8 has been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rezai in view of Ideker, as applied to Claim 1 above, or, in the alternative, over Rezai and Ideker and further in view of Mann et al. (US Publication No. 2002/0055761).

Claim 8 depends from Claim 1. As set forth above, the combination of Rezai and Ideker fails to teach or suggest modulating a portion of the autonomic nervous system based on the determined sympathetic activity/parasympathetic activity ratio so as to treat a female subject for a fertility condition. As Mann is cited solely for its alleged disclosure of stimulating a pelvic nerve (i.e., to treat incontinence, urgency, frequency, or pelvic pain), it fails to remedy the deficiencies of Rezai. Mann does not disclose determining the sympathetic activity/parasympathetic activity ratio of a subject and modulating the ANS of the subject based on the determined sympathetic activity/parasympathetic activity ratio.

Since the combination of Rezai, Ideker and Mann et al. does not disclose this claim element, the references, either alone or combined, do not teach or suggest all the claim limitations of Claim 8.

Therefore, a *prima facie* case of obviousness has not been established because the combination of Rezai in view of Ideker and further in view of Mann fails to teach or suggest all the claimed limitations, namely modulating at least a portion of the autonomic nervous system of a female subject to increase the sympathetic activity/parasympathetic activity ratio in manner effective to treat a female subject for a fertility condition, wherein the modulation is based on the determined sympathetic activity/parasympathetic activity ratio. The Applicants therefore respectfully request that the 35 U.S.C. § 103(a) rejection of Claim 8 be withdrawn.

Claim 19 has been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rezai in view of Ideker, as applied to Claim 1 above, and further in view of Khan et al. (US Publication No. 2002/0064501).

Claim 19 depends from Claim 1. As set forth above, elements of the rejected claims include a method of modulating at least a portion of the autonomic nervous system of a female subject to increase the sympathetic activity/parasympathetic activity ratio so as to treat the female subject for a fertility condition. As described above, the combination of Rezai and Ideker fails to teach or suggest modulating a portion of the autonomic nervous system based on the determined sympathetic activity/parasympathetic activity ratio so as to treat a female subject for a fertility condition.

The addition of Khan does not remedy this deficiency. Khan discloses using an immunoregulator to treat an immune-mediated disorder, including "chronic inflammatory disease, such as diabetes type I or II, rheumatic disease, Sjogrens syndrome, multiple sclerosis, transplantation-related immune responses such as graft-versus-host-disease, post-transfusion thrombocytopenia, chronic transplant rejection, pre-eclampsia, atherosclerosis, asthma, allergy and chronic auto-immune disease, and acute inflammatory disease" (paragraph [0028]). However, Khan does not disclose determining the sympathetic activity/parasympathetic activity ratio

of a subject and modulating the ANS of the subject based on the determined sympathetic activity/parasympathetic activity ratio.

Therefore, Khan does not remedy the deficiencies of the combination of Rezai and Ideker. Consequently, a *prima facie* case of obviousness has not been established because the combination of Rezai, Ideker and Khan fails to teach or suggest all the claimed limitations, namely modulating at least a portion of the autonomic nervous system of a female subject to increase the sympathetic activity/parasympathetic activity ratio in manner effective to treat a female subject for a fertility condition, wherein the modulation is based on the determined sympathetic activity/parasympathetic activity ratio. Therefore, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claim 19 be withdrawn.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Bret Field at (650) 833-7770.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number PALO-004.

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